REMARKS/ARGUMENTS

I. Status of the Claims

Claims 1-137 are currently pending, with claims 1 (in part), 4-13, 17-24, 36, 38-39, 41-45, 51, 55, 57, 59-65, 67, 69-137 withdrawn from consideration as directed to a non-elected invention or species. Upon entry of this amendment, claims 1, 3, 14, 27-28, 34-35, 37 and 48 are amended and claims 78-137 canceled without prejudice or disclaimer. Claims 78-137 are canceled solely because they are directed to non-elected inventions. Applicants reserve the right to reintroduce the unamended or canceled claims in this or another application. Claims 1-77 are thus pending following entry of this amendment.

II. Response to Restriction Requirement

The Office has refused the request to examine claims 41-45 with the currently elected claims. It is noted that claims 1-40 and 46-68, for example, are linking claims that link Group I and Group IV claims. It is thus requested that should one of these linking claims be found allowable, that claims 41-45 be rejoined and fully examined for patentability in accordance with MPEP 809.

With respect to withdrawn claims 4-13, 17-24, 36, 38-39, 41-45, 51, 55, 57, 59-65 and 67, it is noted that these are withdrawn solely as being directed to non-elected species. As such, it is applicants' understanding that the Office in reviewing the amended claims and remarks set forth in this response will follow the procedure set forth in MPEP §803.02, whereby upon the finding of allowable species, examination will continue with the non-elected species until all species have been examined or a non-allowable species is found.

III. Information Disclosure Statement

Documents AN and AO listed on the information disclosure statement mailed March 16, 2001 have not been considered because dates were not listed on the IDS. A supplemental IDS is enclosed that lists these documents and includes the dates. It is requested that the Examiner consider these documents.

Applicants note they have not received a marked-off copy of the information disclosure statement submitted on June 6, 2002 showing consideration of the cited documents by the Examiner. Courtesy copies of this IDS and the documents cited therein are also enclosed. It is requested that these documents also be considered, and that a marked-off copy of the IDS be provided to Applicants with the next communication from the Patent Office.

IV. Claim Rejections under 35 U.S.C. 112

A. Written Description Rejection

Claims 1-3, 14-16, 25-35, 37, 40-50, 52-54, 56, 58, 66 and 68 are rejected under 35 U.S.C. 112, first paragraph for allegedly failing to describe the invention such that one of ordinary skill could determine that the inventors had possession of the invention at the time the application was filed. For the reasons that follow, Applicants respectfully disagree.

The standard for determining whether the written description requirement has been satisfied is to determine whether the specification describes the *claimed invention* in sufficient detail such that one skilled in the art can reasonably conclude that the inventor had possession of the *claimed invention* (see, e.g., MPEP 2163; and Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116). So the key inquiry is whether the *claimed invention* is adequately described. The current claims, as restricted, are directed to screening methods for identifying a substrate of a carrier-type transport protein, not to chemical compounds themselves. Consequently, the appropriate test from a written description standpoint with respect to the current claims is whether one of skill could reasonably conclude that the Applicants were in possession of such *screening* methods at the time the application was filed. It is submitted that the answer to this test is "yes."

Claim 1 as currently pending reads:

> A method of screening for a substrate to a carrier-type transport protein, comprising:

(a) providing a library comprising different complexes, each complex comprising a compound and a reporter, the compound varying between different complexes;

(b) providing a population of cells, one or more of which expresses one or more carrier-type transport proteins;

(c) contacting the population of cells with a plurality of complexes from the library; and

(d) detecting a signal from the reporter of a complex internalized within a cell, wherein the reporter preferentially generates the signal once the reporter is internalized within the cell, the signal thus providing an indication that a complex whose reporter generated the signal comprises a compound that is a potential substrate for a carrier-type transport protein.

Under the Written Description Guidelines (Fed. Reg., vol. 66, page 106, January 5, 2001), the written description requirement can be satisfied by providing a representative number of species to demonstrate that the inventors were in possession of the claimed invention. It is submitted that the application describes a representative number of species with respect to each aspect of the currently pending claims.

For instance, with respect to the nature of the complexes that are screened, the application describes in considerable detail exemplary components for use in the complexes, as well as methods for preparing the complexes (see, e.g., pages 22-28). A number of specific examples for the preparation of various types of complexes are described in the specification, including: a 400 member dipeptide fluorescent peptide library (Examples 2), luciferin dipeptide conjugates (Example 7, section IV), luciferin glycocholic acid conjugates (Example 7, section V), a library of bile acid-luciferin conjugates (Example 7, section VI), and conditionally labeled fluorescent dipeptides (Example 8).

The application also provides extensive discussion regarding appropriate cell types and methods for preparing cells that express one or more carrier-type transport proteins (see, e.g., pages 28-30). An example that describes methods for preparing cells that express a bile acid transporter or a peptide transporter (Example 1) is also included in the specification.

Moreover, the application cites several well-known references that describe established methods in the art that can be utilized to prepare the desired cells (page 30, lines 4-9).

Finally, the application includes extensive discussion on a number of different strategies for conducting the contacting and detecting steps. In fact, the specification discusses in detail at least five different strategies based on the use of conditional reporters alone, as well as providing a corresponding example for many of these approaches. For instance, the application describes detection methods in which:

1) the reporter is a substrate for an intracellular enzyme that forms a detectable signal once it is internalized (see, e.g., pages 32-33; Example 7; and claims 14);

2) the reporter is a masked reporter and generates a strong signal once it is internalized within a cell and the masking group removed (see, e.g., page 33; and Example 8);

3) reporters interact with an intracellular agent to generate a signal (see, e.g., page 34; Example 6; and claims 12);

4) internally quenched reporters are utilized (see, e.g., pages 34-35 and Example 5); and

5) various different bioactive reporters are utilized (see, e.g., pages 35-36; and claims 4, 19, 20 and 22).

Although the foregoing reasons are deemed sufficient to warrant withdrawal of the written description rejection, Applicants nonetheless address the specific issues raised in the Office Action, namely: 1) that the specification lacks adequate guidance on what structural features the complexes share, 2) that the protein and ligands are only described in functional terms, 3) that one cannot determine a priori what complexes are encompassed by the claims, and 4) that the specification lacks adequate examples to describe the complexes.

The primary issue underlying these specific concerns is the assertion that the specification does not provide adequate guidance with respect to the structure of the complexes. In response, it is first reiterated that written description must be analyzed from the standpoint of *what is claimed.* Although the concerns raised in the Office Action might be relevant if the current claims were directed to chemical compositions, the claims currently under examination

are instead drawn to methods for screening compounds, not the compounds themselves. Consequently, the structural detail the Office seeks is unnecessary to satisfy the written description requirement with respect to the current claims. Nonetheless, it is also noted that the specification does in fact provide considerable guidance on the general structure of compounds suitable for screening (see, e.g., pages 22-28 and examples 2, 7 and 8).

Structural details beyond those provided in the current claims and specification are not required because screening methods by definition involve the analysis of widely divergent compounds to identify the limited number of compounds having the desired activity. If the claims are deemed to encompass compounds of divergent structure, this is a reflection of the fact that the essence of a screening method lies in the ability to screen a large number of distinct molecules.

The Office Action cites to University of California v. Eli Lilly and Co. (43 USPQ2d 1398, 1405) ("Lilly") for the proposition that structural detail rather than a functional description must be provided to satisfy the written description requirement. This case, however, addresses issues distinct from those raised here. In Lilly, the claims in dispute were primarily drawn to nucleic acids, i.e., to chemical compositions. The court held that with respect to nucleic acids, the written description requirement could not be satisfied simply by describing functional characteristics. But the current claims are not directed to nucleic acids, nor, in fact, to any type of chemical composition. As such, the decision in Lilly cannot be extrapolated to the present screening claims as the Office Action seeks to do.

The Office Action also asserts that one must be able to "determine a priori" what ligands, compounds and reporters are encompassed by the claims for the written description to be satisfied. In response, it is submitted that the Office Action is 1) applying the wrong standard, and 2) that this standard is inapplicable to the current claims.

The standard is wrong, because, as noted earlier, the standard for assessing written description with respect to a genus claim is whether a representative number of species illustrative of the claimed invention are described. For the reasons set forth above, it is submitted that the answer to this question is yes. There is no legal requirement that one be able to determine "a priori" what substrates will be identified in a screening claim.

The standard is inapplicable because one simply cannot know, in fact one does not want to know, a priori the detailed chemical structure of the compounds to be screened. The power and utility of a screening method lies in the fact that a huge number of widely diverse compounds are screened. Typically, the structure of the compounds being screened is not known. Instead one usually starts with a large population of compounds of unknown structure and, only after a compound with the desired activity is identified, is the structure determined. Applicants also reiterate that the general structural requirements set forth in the claims, coupled with the description and examples provided in the specification, provide sufficient information for one of skill to determine the general structure of suitable complexes for screening.

In response to the final issue, namely that the specification lacks sufficient examples, applicants note that the application in fact includes a large number of examples, with at least examples 1, 3, 5, 6, 7 and 8 being directly relevant to various aspects of the current claims.

B. Enablement

Claims 1-3, 14-16, 25-35, 37, 40-50, 52-54, 56, 58, 66 and 68 are rejected under 35 U.S.C. 112, first paragraph. Although these claims are said to be enabled with respect to screening dipeptide libraries and libraries of glycocholic derivatives to identify ligands for the PEPT1 and ileal bile acid transporter, they are said not to be enabled across their entire scope. The primary assertion is that the specification lacks sufficient guidance with respect to the type of ligands, reporters and transport proteins that should be used. As a consequence, it is alleged that many complexes might not be transported into the cells.

In response, it is submitted that this concern is unwarranted with respect to screening claims. Those conducting screening analyses understand that the vast majority of the compounds being screened will not have the desired activity. As discussed above, the primary goal in a typical screening method is to rapidly assay a diverse collection of compounds to identify the limited number that have the desired activity. By requiring that Applicants identify in advance what complexes are likely to be a ligand for a transport protein, the Office negates the

purpose of a screening method, namely to identify active ligands from a population of diverse compounds whose structure is typically not known.

The case law on enablement is also clear that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (see, e.g., MPEP 2164.01 and *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom.* Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). Those conducting screening methods recognize that as a matter of course that many different large populations of complexes must be prepared and then assayed to identify those complexes with the desired activity. Thus, it does not follow that because many or most of the complexes might not be active that the enablement requirement is not satisfied. Furthermore, as described at length with respect to the written description rejection, the specification does in fact provide numerous examples and considerable description regarding suitable complexes that might be screened.

The Office Action on page 15 suggests that the specification does not discuss methods for determining whether a complex simply binds to a cell (e.g., because the reporter prevents uptake) or is transported into the cell. This is not the case. The specification discusses at length a number of different strategies for distinguishing between complexes that simply bind to the exterior of a cell and complexes that are actually taken up by the cell (see, e.g., pages 31-36; see also the summary of 5 strategies listed in the written description section above).

V. Claim Rejections under 35 U.S.C. 112, second paragraph

Claims 1-3, 14-16, 25-35, 37, 40-50, 52-54, 56, 58, 66 and 68 are rejected under 35 U.S.C. 112, first paragraph because the phrase "carrier-type transport protein" is said to be defined only in functional terms rather than by common structural features. In response, it is first noted that this term is well recognized in the art. The term is also specifically defined both in the background section (see, e.g., page 1, line 28 to page 2, line 4) and in the definition section, which also lists numerous specific examples of carrier-type transport proteins (see, e.g., page 9, line 30 to page 10, line 11). Based upon knowledge common in the art and these descriptions, it is submitted that one skilled in the art would readily recognize what proteins are encompassed by

the current claims. That the term is recognized in the art is illustrated, for example, in the attached article by Alberts et al. (1998) "Comparison of passive and active transport", Garland Publishing (http://www.accessexcellence.org/AB/GG/passActiveTrans.html).

The Office Action also states that a "claim to a material" that is defined solely in functional terms does not particularly point out the claimed invention. As this statement itself points out, however, this rule applies to *materials that are claimed.* The current claims, however, are not directed to materials but screening methods. Thus, the rule the Office Action seeks to apply is inapplicable to the current claims.

VI. Claim Rejections under 35 U.S.C. 102

Claims 1, 2, 35, 37, 56, 58, 66 and 68 are said to be anticipated by Abe et al. (Abe, H. (1998) Bioconjugate Chem. 10:24-31; "Abe"). Abe is said to discuss a method of screening certain fluorescently or radiolabeled dipeptides or analogues against PEPT1, a dipeptide carrier-type transporter.

In response, it is noted that claim 1 has been amended to include the element previously set forth in claim 2. The claim thus requires that the reporter preferentially generates a detectable signal once it is internalized within the cell. Abe does not discuss a method in which a reporter preferentially generates a signal once it is internalized. For example, there is no indication in the Abe reference that the fluorescent or radioactive labels utilized in his experiment would preferentially generate a signal once incorporated into a cell expressing a carrier-type transport protein. Abe thus fails to teach each and every aspect of the current claims as required for an anticipation rejection. It is thus requested that this ground of rejection be withdrawn.

Claims 1-3, 14, 35, 56 and 66 are said to be anticipated by Swaan et al. (Swann, P.W., et al. (1997) Bioconjugate Chem. 8:520-525; "Swaan"). Swaan is said to discuss screening radiolabled bile acid-peptide conjugates against a bile acid transporter expressed in CaCo-2 cells. Swaan is also said to discuss intracellular cleavage of the substrates by peptidases.

Swaan also fails, however, to discuss a method in which a reporter preferentially generates a signal once it is internalized. To the contrary, the radioactive label used in Swann

would be expected to give the same type of signal whether located outside or inside the cell. Accordingly, Swaan does not anticipate the currently pending claims.

VII. Claim Rejections under 35 U.S.C. 103

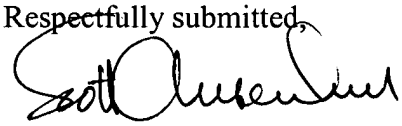
Claims 1-3, 14, 35, 56, 66 and 68 are said to obvious over Swaan in view of Dawson et al. (U.S. Patent No. 5,589,358). Swaan is cited for the reasons described above; Dawson is said to discuss screening methods that utilize controls.

But even when these two references are combined, they fail to teach each and every element of the present claims because Dawson fails to remedy the deficiencies in the disclosure of Swaan. In particular, neither of these cited references teaches or suggests a screening method is which a reporter preferentially generates a signal once it becomes incorporated into a cell. Accordingly, it is submitted that the claims are not prima facie obvious based upon the combined disclosure of these two references.

If the Office concludes in view of the foregoing remarks that these cited references do not anticipate the current claims or render them obvious, then it is requested that the Office continue examination of the withdrawn claims which are directed to non-elected species in accordance with MPEP 809.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 303-571-4000.

Respectfully submitted,



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Attachments
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